Series 11, Number 3 September 2010

President's Council on Fitness, Sports & Nutrition

Research DIGEST

Published quarterly by the President's Council on Fitness, Sports & Nutrition Washington, D.C.

Guest Authors

Melinda L. Irwin, PhD, MPH
Associate Professor of Epidemiology and Public Health
Yale School of Public Health

Stephanie M. George, PhD, MPH, MA
Nutritional Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute

Charles E. Matthews, PhD
Nutritional Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute

Co-editors

Michael La Monte, PhD
University of Buffalo
The State University of New York

Barbara Ainsworth, PhD
Arizona State University

David Bassett, Jr., PhD
University of Tennessee

Physical Activity and Breast Cancer: Prevention, Survival, and Mechanisms

Introduction

In the last three decades we have made considerable progress in combating breast cancer, and during this time physical activity has emerged as an important modifiable health behavior that can play a key role in both the prevention and treatment of this disease. In this report we will highlight the role of two pioneering researchers in developing the hypothesis that physical activity can prevent breast cancer and review briefly the data that forms the evidence base for the inverse association between physical activity and breast cancer. In addition, we will examine the biological mechanisms through which physical activity may influence the natural history of breast cancer, and examine the rapidly growing body of research that demonstrates the important role for physical activity/exercise programs among breast cancer survivors.

Breast Cancer Epidemiology

Breast cancer is the second leading cause of cancer death among women in the United States. In 2009 more than 192,000 women were diagnosed with invasive breast cancer, and about 40,000 died from the disease (1). Trends in the incidence of breast cancer have been influenced in recent years by a number of factors including increased access to screening mammography, the obesity epidemic, and most recently cessation of hormone replacement therapy by many postmenopausal women. Since 2001, incidence rates have trended downward, and further advances in improving survival following a breast cancer diagnosis can be linked to improved treatment regimens, such as new chemotherapeutic agents, and hormone and biological therapies (e.g., tamoxifen, aromatase inhibitors). The proportion of women that live for five or more years after being diagnosed with breast cancer has increased from 75% in 1975 to about 90% currently. In 2006 it was estimated that there were more than 2.5 million breast cancer survivors in the United States. A common definition of "cancer survivor" is any individual who has had a diagnosis of cancer, from the point of diagnosis and for the balance of her life.

Evolution of the Physical Activity–Breast Cancer Hypothesis

There are few modifiable risk factors for breast cancer. Early evidence that linked obesity and reproductive factors, such as age at menarche and menopause, to risk for breast cancer led researchers to focus on modifiable behaviors that may influence these factors. Dr. Rose Frisch was among a small group of population scientists that developed the physical activity–breast cancer hypothesis in the early 1980s. Her research program focused on determinants of female fertility and menstrual dysfunction, and in particular on the affects of energy intake, physical activity, and body weight (fat) on reproductive health. In 1985, her group was first to publish findings investigating the potential association between physical activity and breast cancer.

Dr. Frisch conducted a retrospective cohort study among female college alumnae that compared the prevalence of breast cancer between women who participated in college athletics and women that did not participate in sports or athletics in college (2). As she noted, the "remarkable result" was that the prevalence of breast cancer in the non-athletes was about twice that of the college athletes (Odds ratio = 1.86 [95% CI: 1.00-3.47]). The athletes were also noted to have a later age at menarche, earlier menopause, and were leaner than non-athletes and these factors were proposed as possible biological mechanisms underlying the association observed (2).

Interestingly, the women who reported participating in college athletics were lifelong exercisers. Eighty-two percent of the athletes reported sport participation prior to going to college, and a subsequent report from this study indicated that 74% of them maintained their exercise participation into mid-life (2, 3). Dr. Frisch's other studies in this era were conducted among ballet dancers, elite oarswomen, and in a unique case study, she examined the metabolic, endocrine, and reproductive changes as a 24 year old woman trained for and completed a swim of the English Channel (2). In response to training, changes in insulin secretion and reproductive hormones that, as we will discuss in subsequent sections of this report, would be consistent with reduced risk for breast cancer.

The next major advance in the physical activity–breast cancer hypothesis was made by another avid swimmer, Dr. Leslie Bernstein. Her 1994 study (4) examining the role of lifelong exercise participation and breast cancer risk in young women (< 40 yrs) was a landmark study that ignited research on the role of physical activity and breast cancer in particular, and physical activity and cancer in general. Dr. Bernstein trained in a group at the University of Southern California that was instrumental in developing the science regarding the role of estrogen and progesterone levels in the development of breast cancer and that highlighted the importance of the number of ovulatory cycles during a woman's reproductive years as a determinant of breast cancer risk, owing to the exposure of the breast tissue to both estrogen and progesterone in the second half, the luteal phase, of the menstrual cycle (5).

Dr. Bernstein conducted a case-control study in Los Angeles, CA from 1983 to 1989, which compared lifetime histories of exercise participation between 545 breast cancer cases to a similar number of women without breast cancer (controls) that were matched to cases on age, race, number of pregnancies, and the neighborhood in which they lived. She reported a strong inverse relationship between levels of lifetime exercise and estimated that women who exercised for 3.8 hour/week or more had about a 60% reduction in risk for breast cancer compared to women who reported no exercise participation (Odds ratio = 0.42 [95% CI: 0.27-0.64]).

Since these reports were published, more than 60 epidemiologic studies have examined the physical activity and breast cancer hypothesis and the accumulated evidence was sufficiently compelling that Physical Activity Guidelines for Americans 2008 indicated that there is strong evidence that physical activity may prevent breast cancer. A recent review by Friedenreich and Cust 2008 (6) noted that 47 of 62 (76%) studies examined indicated a protective association between higher levels of physical activity and incident breast cancer. The average risk reduction among more active compared to less active women was 25 to 30%. Furthermore, there was substantial evidence for a dose-response relationship in 28 of 33 studies that examined this issue. That is, there was consistent evidence that intermediate levels of activity provide some benefit, and higher levels provide more protection. The protective association between physical activity and risk for breast cancer appeared to be stronger for long-term or lifetime exercisers, postmenopausal women, and those with a lower body mass index. Importantly, the protective association has been noted in women of nearly every racial and ethnic background.

Recent studies also were noted for their indication that the protective effect of higher levels of physical activity were seen in women with tumors that were more dependent on hormones (estrogen and progesterone positive tumors), which typically accounts for about two-thirds of the breast cancer cases in this country, as well as tumors that were not strongly linked to hormones (hormone negative tumors). These data suggest an important role for biological mechanisms that are outside the classical hormonal pathways leading to many breast cancers. Current research on the physical activity–breast cancer hypothesis is focused on elucidating more specifically the timing in a woman's life, type of exercise, and dose (frequency, intensity) of activity that may provide benefit, as well as a better understanding of the biological mechanisms through which physical activity may exert its protective effects. Next, we examine information regarding these mechanisms that has been developed in both healthy women and breast cancer survivors in recent years.

Biological Mechanisms Explaining the Relationship between Physical Activity and Breast Cancer

A number of mechanisms have been proposed to explain the ability of higher levels of physical activity to prevent breast cancer, reduce risk of cancer recurrence, or improve overall survival following a breast cancer diagnosis, and these mechanisms include the beneficial effects of activity on hormonal exposures, insulin and insulin-like growth factors (IGFs), as well as other obesity-related factors (e.g., adipokines, inflammation), and immune function (7, 8).

Sex Hormones

Changes in sex hormones are perhaps the most consistently cited potential mechanism for the association between physical activity and breast cancer. As noted above female sex hormones are an important factor in the development of breast cancer, and in premenopausal women exposure to both estrogen and progesterone in the luteal phase of the menstrual cycle are believed to be the important exposures. Higher levels of physical activity, particularly when energy intake does not compensate for energy expended during exercise, have been demonstrated to shorten the length of the luteal phase, progesterone levels, and can increase the number of anovulatory cycles a woman experiences (9), all of which would be predicted to reduce her risk for breast cancer.

In postmenopausal women the primary source of estrogens in circulation are derived from the conversion of adrenal androgens to estrogens by the aromatase enzyme which is found in great abundance in adipose/fat tissue (10). Androgens, such as testosterone, also may play a role in breast cancer. Recent analysis of nine cohort studies showed that the risk for breast cancer increased significantly with increasing concentrations of estradiol, free estradiol, and estrone (all forms of estrogen) in postmenopausal women (26). Elevated testosterone levels were also associated with increased risk for primary and secondary breast cancer risk in both premenopausal and postmenopausal women (26,28).

Another factor involved in the hormonal link to breast cancer is sex hormone binding globulin (SHBG) which is a protein complex that acts as a carrier of hormones in circulation. Levels of SHBG in circulation are variable and lower levels of these proteins result in more hormone being available to breast tissue (i.e., greater "bioavailability"). As we will describe below, hyperinsulinemia is associated with lower levels of physical activity and/or elevated adiposity and can reduce production of SHBG in the liver, leading to a greater bioavailability of hormones in circulation. Thus, higher levels of physical activity may influence a woman's long-term exposure to sex hormones early in life by exerting an influence on the menstrual cycle or via SHBG, or by minimizing weight gain during adulthood and therefore reducing the potential for the elevated estrogen exposures late in life associated with body fat. McTiernan and colleagues (10) examined the influence of a 12-month exercise program in postmenopausal women on these hormonal factors and found that exercise decreased serum estrogens and androgens, and increased SHBG resulting in lower amounts of free, active estrogens and androgens. Women who lost more body fat with exercise were noted to have larger changes.

Insulin and Insulin-like Growth Factors

Insulin and insulin-like growth factor-1 (IGF-I) both can exert growth promoting effect on breast cancer cells, and therefore are believed to be important mechanisms associated with the development of breast cancer. Insulin and IGF-1 can enhance tumor development by stimulating cells to multiply and inhibiting cells from dying, or undergoing programmed cell death (i.e., apoptosis (11, 12, 13)). Similar to SHBG and sex hormones discussed previously, insulin-like growth factor binding proteins (IGFBP) are important determinants of the bioavailability of IGF-1, and IGFBP-3 is an important carrier of IGF-1 in circulation. IGFBP-3 also may either stimulate or suppress cells from multiplying by restricting the availability and biological activity of IGF-I (11, 12). Although the data are not consistent, high levels of IGF-I and low levels of IGFBP-3 have been associated with an increased risk of breast cancer and adverse prognostic factors after a diagnosis of breast cancer (14, 15, 16).

Similarly, indicators of hyperinsulinemia have also been linked to increased risk for breast cancer (17), as well as survival among breast cancer survivors (18, 19, 20). The strong association between fasting insulin levels and breast cancer death has led a number of oncologists and scientists to consider the targeting of insulin as a therapeutic modality among breast cancer survivors, particularly because insulin can be modified by lifestyle and pharmacologic interventions. There is considerable evidence demonstrating the benefits of exercise participation on insulin metabolism. Irwin and colleagues showed that moderate-intensity aerobic exercise, such as brisk walking, performed on average for 120 min/wk over six months was associated with a 25% decrease in insulin and 7% decrease in IGF-1 among exercisers, and a 5% increase in insulin and 2% increase in IGF-1 among controls (21). Given that high insulin levels promote the synthesis and activity of IGF-I via increases in insulin-mediated changes in IGFBP-3 concentrations, decreases in insulin would be predicted to favorably influence IGF levels.

Obesity and Weight Gain:

The association of obesity with breast cancer risk is qualitatively different for pre- and postmenopausal women. Obese premenopausal women are not at increased risk and may be provided some protection from breast cancer owing to the relationship between obesity and anovulatory menstrual cycles. In contrast, obese

postmenopausal women are at increased risk that is associated with elevated estrogen levels (22). A 2008 meta-analysis of 31 prospective studies in postmenopausal women found a 12% increase in breast cancer risk for every 5kg/m2 increase in BMI (e.g., an increase in BMI from 25 to 30) (23). While aerobic exercise has been associated with favorable changes in body fat, especially intra-abdominal or visceral body fat, in healthy women (24); fewer trials have examined the effect of exercise on outcomes of body composition in breast cancer survivors. In a recent publication, moderate-intensity aerobic exercise, such as brisk walking, performed for approximately 120 min/wk, was associated with modest, yet favorable, changes in body fat in postmenopausal breast cancer survivors (25).

Many studies over the past 30 years have shown that women who are overweight or obese when they are diagnosed with breast cancer are also more likely to experience a recurrence or die from breast cancer than women who are of a normal weight (16). A recent study suggested that approximately 30%-50% of breast cancer deaths among postmenopausal women in the US can be attributable to being overweight (26). Similarly, in an analysis of obesity on breast cancer survival in premenopausal women, Daling and colleagues reported that women younger than 45 years of age who had invasive breast cancer and a BMI > 25 kg/m2 were 2.5 times as likely to die of their disease within five years of diagnosis compared with women with a BMI < 21 kg/m2 (27).

Research also suggests that women who gain weight after breast cancer diagnosis are at increased risk for breast cancer recurrence and death as compared to women who maintain their weight after diagnosis (17,18). (28). Analyses from a recent study showed that weight gain after diagnosis (~5 to 10 lbs) was related to approximately 50% higher rates of breast cancer recurrence and death (29). However, several recent studies have called these findings into question (19). In studies where chemotherapy was dosed by actual rather than ideal body weight, the association between excess body weight and poor prognosis has not been seen (17,19). Thus, mechanisms other than BMI or weight loss may explain the benefit of physical activity on survival after a breast cancer diagnosis.

However, weight gain may still have adverse affects on risk of other new cancers and overall survival. Specifically, there is evidence that cancer survivors die of noncancer causes at a higher rate than persons in the general population (deaths being primarily from cardiovascular disease and diabetes) (30). Therefore, surviving cancer requires that patients not only treat the primary cancer, but also avoid second cancers for which they are at increased risk. To improve overall survival, it is important for cancer survivors to prevent overweight and obesity via increased physical activity or dietary-induced weight loss. (31)

Leptin and Adiponectin

Two additional hormones that may explain the relationship between physical activity and breast cancer include leptin and adiponectin. Adipose (fat) tissue is the primary source of leptin and a determinant of circulating leptin levels in the body (32, 33, 34, 35). A growing number of publications have provided support for leptin as a breast cancer risk factor, either by direct effects on breast cancer cells, or indirectly by increasing estrogen or promoting insulin resistance (8). Evidence from various prospective trials of postmenopausal women supports the relationship between higher physical activity and decreased leptin (36, 37, 38, 39), especially for exercise training of longer duration and higher intensities (40). Thus, this mechanism is biologically plausible, but the evidence from studies relating leptin to postmenopausal breast cancer incidence is not consistent (8).

In contrast to leptin, adiponectin, a hormone produced by adipocytes (fat cells) is involved in metabolism and inflammation (41, 42, 43). Adiponectin has a strong inverse correlation with fat mass (44); under conditions of obesity, adiponectin concentrations are reduced (45). For this reason, adiponectin is gaining recognition as an interesting and strongly predictive indicator of abdominal fat and its consequences, such as metabolic syndrome (30), outcomes which may also be influenced by physical activity. Among postmenopausal women, an inverse relationship between circulating adiponectin levels and breast cancer risk has been observed (46).

Few trials have examined the effects of physical activity on leptin or adiponectin in breast cancer survivors. Recently, Irwin and colleagues examined the effect of six months of moderate-intensity aerobic exercise vs. usual care on leptin and adiponectin levels in 75 breast cancer survivors (47). Baseline correlations between leptin, adiponectin, and measures of adiposity were strong and consistent with available literature; however the intervention did not result in statistically significant differences in levels of leptin or adiponectin between exercisers and usual care participants. Future research must examine the nature of the relationship between exercise, adiposity, and adipokines in breast cancer survivors, and determine whether exercise alone is sufficient to cause favorable changes in these hormones, which are highly correlated to adiposity, or if greater weight loss (with the addition of a low-calorie diet) is necessary to see favorable effects on adipokines.

Inflammation

Biomarkers of low-grade chronic inflammation, such as C-reactive protein (CRP), serum amyloid A (SAA), tumor necrosis factor-α (TNF-α), and interleukin (IL)-6, have been linked with increased cancer risk (48). Although there is limited epidemiologic literature on inflammation and breast cancer risk

(8), these biomarkers of inflammation may affect breast cancer through their effects on apoptosis, cell proliferation, angiogenesis, and metastasis (49). There is evidence that physical activity might reduce chronic inflammation alone, or by reducing body weight or composition (7), given that inflammatory factors have been shown to correlate with body fat (45).

Chronic inflammation has also been associated with higher rates of recurrence and death for several cancers including breast cancer (50, 51). Breast cancer patients have been shown to have elevated concentrations of CRP prior to surgery, and CRP is higher in women with more advanced stage of disease (52). Little is currently known about the effect of physical activity on CRP, IL-6, and TNF-α in breast cancer survivors.

Physical Activity among Breast Cancer Survivors

As survival has increased following diagnosis, women who have experienced breast cancer treatments are facing unique physical and psychological challenges associated with this experience. While many of the acute effects of surgery and adjuvant treatments, such as chemotherapy and radiation, resolve soon after the treatment ends, other symptoms and/or health problems can persist for months and years after treatment, and some health conditions associated with treatment may not emerge until long after the initial treatment has ended (e.g., lymphedema, osteoporosis) (53). Cancer treatment often results in a decrease in physical activity and deconditioning associated with disuse of muscles. Thus, it is important to determine whether exercise training improves muscular strength in cancer survivors.

Recent reviews have reported clear benefits of physical activity for cardiovascular fitness and muscular strength among cancer survivors and modest outcomes with respect to reducing fatigue or improving mood or quality of life (53). Most published exercise trials in breast cancer survivors have examined the impact of exercise on psychosocial outcomes and fitness and have demonstrated that exercise is safe in this population and produces beneficial effects on quality of life, fitness and cancer-related symptoms.

Cancer-related fatigue is one of the most commonly reported side effects of cancer and the related treatments, and is not predictable by cancer site or tumor type. Cancer-related fatigue is unique from other types of fatigue in its persistence and severity (54). The effects of physical activity interventions on cancer-related fatigue have been tested in numerous randomized clinical trials, the majority of which found positive improvements.

In one of the largest studies to date, Courneya and colleagues examined the effects of aerobic exercise alone, resistance exercise alone, or usual care, on fitness, muscular strength, body composition, and quality of life in 242 breast cancer survivors initiating chemotherapy (55). There were significant favorable effects of both aerobic and resistance exercise on multiple outcomes including self esteem, fitness, and body composition, as well as increased chemotherapy completion rates compared with usual care. Furthermore, no significant adverse events were reported; lymphedema did not increase or was not exacerbated by aerobic or resistance exercise. Recently, other clinical trials of women with breast cancer have shown no increased risk for or exacerbation of lymphedema from either aerobic and/or resistance exercise (56). Courneya and colleagues also completed a similar trial of aerobic exercise vs. usual care in breast cancer survivors who had completed adjuvant treatment, and observed similar favorable effects of exercise on fitness and overall quality of life (57).

In a recent roundtable of the American College of Sports Medicine, it was concluded that although there are specific risks associated with cancer treatments that need to be considered when survivors exercise, there seems to be consistent evidence that exercise is safe during and after cancer treatment (53). Exercise training-induced improvements can be expected concerning aerobic fitness, muscular strength, quality of life, and fatigue in breast cancer survivors (53).

Physical Activity and Breast Cancer Survival

Four large observational studies have recently been published demonstrating that participation in moderate-intensity recreational physical activity after diagnosis is associated with improved survival in women who develop breast cancer (58, 59, 60, 61). These studies have demonstrated a 24-67% reduction in the risk of total deaths and 50-53% reduction in the risk of breast cancer deaths in women who are physically active after breast cancer diagnosis compared with women reporting no recreational physical activity. Throughout these studies, the decreased risk of death, especially overall death, associated with physical activity was observed in pre- and postmenopausal women, overweight and normal weight women, and women with stage I-III disease.

Table 1. Recommended levels of physical activity in relation to breast cancer prevention and treatment

Age or Health Status	Aerobic Activity		Muscle & Bone Strengthening
For Breast Cancer Prevention	***Moderate***	***Vigorous***	
Children and Adolescents (6-17 yrs)	1 hr./day	At least 3 days/week	3 days/week of each
Adults (18+ yrs)	150 min./week	75 min./week	2 days/week muscle strengthening
	Equivalent combinations of moderate or vigorous activity are permissible. *Additional health benefits, and better weight maintenance, may be obtained by doing twice the recommended levels.*		

After a Breast Cancer Diagnosis	
After Surgery	Resume normal daily activities and exercise as quickly as possible, following your surgeon's recommended timeline.
During Chemotherapy and/or Radiation	Continue normal daily activities and exercise as much as possible during treatment, but adjust your routine as effects of treatment dictate. Consult with your physician as needed.
After Initial Treatment Has Ended	Strive to meet recommended levels of activity, but if not possible due to your fitness level or a health condition, try to be as physically active as your abilities allow. Consult with your physician as needed.
Special Considerations	Surgery and radiation treatment may adversely affect flexibility in the upper body. Adjustments to exercise routine may be required. Also, women with metastatic breast cancer may be at increased risk for bone fractures, so gradual progression of exercise amounts may be required. Women with metastatic disease should discuss their exercise program with their oncologist.

While any amount of recreational physical activity performed after diagnosis was associated with a decreased risk of death, the maximal benefit occurred in women who performed the equivalent of brisk walking three hours per week. Given that women who are more physically active after diagnosis may have been more active before diagnosis, these studies cannot exclude the possibility that physically active women develop breast tumors that are biologically less aggressive.

These observational findings of post-diagnosis physical activity and improved survival suggest that exercise may confer additional improvements in breast cancer survival beyond surgery, radiation and chemotherapy. However, despite this growing body of observational evidence suggesting a strong link between physical activity and breast cancer survival there is still the potential for unknown or poorly characterized factors to confound these associations. For example, women who participate in higher levels of physical activity may engage in many other healthy behaviors that contribute to reduced risk, or they may be more adherent to their cancer treatments.

Conclusions

Physical activity has been shown to be a beneficial behavior for the prevention of breast cancer and many other common chronic diseases. For general health promotion, engaging in 150 minutes per week of moderate-to-vigorous intensity physical activity (example: brisk walking), 75 minutes per week of vigorous intensity activity (example: running) or an equivalent combination of both is recommended for adult women. The biological mechanisms through which physical activity may confer protection include: a favorable influence on sex hormones, insulin-related pathways, the prevention of weight gain and obesity, and potential effects on adipokine levels and inflammatory pathways.

Regarding physical activity after a diagnosis of breast cancer, one of the most common questions cancer survivors ask is: "What can I do to improve my survival?" (62). As with preventing cancer, physical activity has been shown to have a multitude of health benefits (31) for living well after cancer, and importantly, it is a behavior women can change and has been shown to be safe. With specific exercise programming adaptations based on disease and treatment-related adverse effects, cancer survivors are encouraged to follow the physical activity guidelines developed for the general population. (54) Even in cancer patients with existing disease or undergoing difficult treatments, avoiding inactivity (e.g., decreasing time spent sitting) is likely to be helpful (53).

> *"Regular participation in exercise during adolescence and throughout adulthood can help reduce a woman's risk of developing breast cancer, and among breast cancer survivors, regular exercise can improve side effects of treatment, and may increase survival."*

References

1. American Cancer Society. Breast Cancer Facts and Figures 2009-2010. Atlanta, GA, 2009.
2. Frisch RE, Hall GM, Aoki TT, et al. Metabolic, endocrine, and reproductive changes of a woman channel swimmer. Metabolism 1984;33:1106-11.
3. Wyshak G, Frisch RE. Breast cancer among former college athletes compared to non-athletes: a 15-year follow-up. Br J Cancer 2000;82:726-30.
4. Bernstein L, Henderson BE, Hanisch R, et al. Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst 1994;86:1403-8.
5. Pike MC, Spicer DV, Dahmoush L, et al. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev 1993;15:17-35.
6. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. British Journal of Sports Medicine 2008;42:636-47.
7. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer 2008;8:205-11.
8. Neilson HK, Friedenreich CM, Brockton NT, et al. Physical Activity and Postmenopausal Breast Cancer: Proposed Biologic Mechanisms and Areas for Future Research. Cancer Epidemiol Biomarkers Prev 2009;18:11-27.
9. Loucks AB. Energy availability, not body fatness, regulates reproductive function in women. Exerc Sport Sci Rev 2003; 31:144-8.
10. McTiernan A, Tworoger SS, Ulrich CM, et al. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. Cancer Res 2004;64:2923-8.
11. Gray SG, Stenfeldt Mathiasen I, De Meyts P. The insulin-like growth factors and insulin-signalling systems: an appealing target for breast cancer therapy? Horm Metab Res 2003;35:857-71.
12. Yu H, Rohan, T.. Role of the insulin-like growth factor family in cancer development and progression. Journal of Natl Cancer Inst. 2000; 92 (18):1472-89.
13. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 2001;60:91-106.
14. Hankinson S, Willett, WC., Colditz, GA., Hunter, DJ., Michaud, DS., Deroo, B., et al. Circulating concentrations of insulin-like growth factor-1 and risk of breast cancer. Lancet.1998;351:1393-1396.
15. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.
16. 16. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes and Control 2002; 13:741-51.
17. Neilson H, Friedenreich C, Brockton N, et al. Physical activity and postmenopausal breast cancer: Proposed biologic mechanisms and areas for future research. Cancer Epidemiol Biomarkers Prev 2009;18:11-27.
18. Goodwin PJ, Ennis M, Pritchard KI, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 2002;20:42-51.
19. Irwin ML BL, McTiernan A, et al. Associations between fasting c-peptide and breast cancer death: The Health, Eating, Activity, and Lifestyle (HEAL) Study. J Clin Oncol; In Press.
20. Pollak MN CJ, Shepherd L, et al. Insulin resistance, estimated by serum C-peptide level, is associated with reduced event-free survival for postmenopausal women in NCIC CTG MA.14 adjuvant breast cancer trial. J Clin Oncol 24:9s, 2006 (suppl 18S, abstr 524).
21. Irwin ML, Varma K, Alvarez-Reeves M, et al.. Randomized controlled trial of exercise on insulin and IGFs in breast cancer survivors: The Yale Exercise and Survivorship Study. Cancer Epidemiol Biomarkers Prev 2009;18(1):306-13.
22. Goodwin PJ, Pritchard KI. Obesity and hormone therapy in breast cancer: an unfinished puzzle. J Clin Oncol 2010;28:3405-7.
23. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. The Lancet 2008;371:569-78.
24. Irwin ML, Yasui Y, Ulrich CM, et al. Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA 2003;289:323-30.
25. Irwin ML, Alvarez-Reeves M, Cadmus L, et al.. Randomized controlled trial of exercise on body fat, lean mass, and bone mineral density in breast cancer survivors. Obesity 2009;17(8):1534-41.
26. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. New Engl J Med 2003;348:1625-38.
27. Daling JR, Malone KE, Doody DR, et al. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001;92:720-9.
28. Irwin ML, McTiernan A, Baumgartner RN, et al. Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. J Clin Oncol 2005;23:774-82.
29. Kroenke CH, Chen WY, Rosner B, et al. Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 2005;23:1370-8.
30. Carver JR, Shapiro CL, Ng A, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol 2007;25:3991-4008.
31. U.S. Department of Health and Human Services: Physical activity and health: A report of the Surgeon General. Atlanta, National Center for Chronic Disease Prevention and Health Promotion, 1996.
32. Garofalo C, Koda M, Cascio S, et al. Increased expression of leptin and the leptin receptor as a marker of breast cancer progression: possible role of obesity-related stimuli. Clin Cancer Res 2006;12:1447-53.
33. Garofalo C, Surmacz E. Leptin and cancer. J Cell Physiol 2006;207:12-22.
34. Sulkowska M, Golaszewska J, Wincewicz A, et al. Leptin--from regulation of fat metabolism to stimulation of breast cancer growth. Pathol Oncol Res 2006;12:69-72.
35. Surmacz E. Obesity hormone leptin: a new target in breast cancer? Breast Cancer Res 2007;9:301.
36. Frank LL, Sorensen BE, Yasui Y, et al. Effects of exercise on metabolic risk variables in overweight postmenopausal women: a randomized clinical trial. Obes Res 2005;13:615-25.
37. Giannopoulou I, Fernhall B, Carhart R, et al. Effects of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. Metabolism 2005;54:866-75.

38. Hayase H, Nomura S, Abe T, et al. Relation between fat distributions and several plasma adipocytokines after exercise training in premenopausal and postmenopausal women. J Physiol Anthropol Appl Human Sci 2002;21:105-13.
39. Kohrt WM, Landt M, Birge SJ, Jr. Serum leptin levels are reduced in response to exercise training, but not hormone replacement therapy, in older women. J Clin Endocrinol Metab 1996;81:3980-5.
40. Hulver MW, Houmard JA. Plasma leptin and exercise: recent findings. Sports Med 2003;33:473-82.
41. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;115:911-9; quiz 20.
42. Kumada M, Kihara S, Ouchi N, et al. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation 2004;109:2046-9.
43. Wolf AM, Wolf D, Rumpold H, et al. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochem Biophys Res Commun 2004;323:630-5.
44. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.
45. Vona-Davis L RDAae, paracrine, and autocrine factors in breast cancer risk and progression. Endocrine-Related Cancer 2007:14:189-206.
46. Miyoshi Y, Funahashi T, Kihara S, et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res 2003;9:5699-704.
47. Irwin ML, Mayne ST. Cancer J. 2008;14(6):435-41.
48. Il'yasova D, Colbert LH, Harris TB, et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev 2005;14:2413-8.
49. DeNardo DG, Coussens LM. Inflammation and breast cancer. Balancing immune response: crosstalk between adaptive and innate immune cells during breast cancer progression. Breast Cancer Res 2007;9:212.
50. Ardizzoia A LP, Brivio F, et al. Tumor necrosis factor in sold tumors: increased blood levels in metastatic disease. Journal of Biological Regulations and Homeostatic Agents 1992;6(103).
51. Pierce BL, Neuhouser ML, Wener MH, et al. Correlates of circulating C-reactive protein and serum amyloid A concentrations in breast cancer survivors. Breast Cancer Res Treat 2008.
52. McMillan DC EM, Sattar N, Angerson WJ, Johnstone J, McArdle CS. Measurement of the systematic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer. Nutrition and Cancer 2001;41(1&2):64-9.
53. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors. Medicine & Science in Sports & Exercise 2010; 42:1409-26.
54. Ryan JL, Carroll JK, Ryan EP, et al. Mechanisms of cancer-related fatigue. Oncologist 2007;12 Suppl 1:22-34.
55. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol 2007;25:4396-404.
56. Ahmed RL, Thomas W, Yee D, et al. Randomized controlled trial of weight training and lymphedema in breast cancer survivors. J Clin Oncol 2006;24:2765-72.
57. Courneya KS, Mackey JR, Bell GJ, et al. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol 2003;21:1660-8.
58. Holmes MD, Chen WY, Feskanich D, et al. Physical activity and survival after breast cancer diagnosis. JAMA 2005;293:2479-86.
59. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:379-86.
60. Irwin ML. Influence of pre- and post-diagnosis physical activity on survival in breast cancer survivors: the Health, Eating, Activity, and Lifestyle (HEAL) Study. Journal of Clinical Oncology 2008;26(24):3958-64.
61. Sternfeld B, Weltzien E, Quesenberry CP, Jr., et al. Physical activity and risk of recurrence and mortality in breast cancer survivors: findings from the LACE study. Cancer Epidemiol Biomarkers Prev 2009;18:87-95.
62. Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin 2006;56:323-53.